

## HEALTH EFFECTS ATTRIBUTED TO RADON FROM THE PERSPECTIVE OF THE LINEAR NO-THRESHOLD HYPOTHESIS\*

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The linear no-threshold hypothesis (LNT) is a model of the damage caused by ionizing radiation which presupposes that the response is linear at all dose levels. Thus, LNT asserts that there is no threshold of exposure below which the response ceases to be linear. While most authorities agree that the LNT model is most appropriate, the advances in radiobiology during the past two decades, the understanding of carcinogenesis, and the discovery of defenses against carcinogenesis challenge the validity of the LNT model. These studies disagree with the LNT hypothesis suggesting that low levels of low LET radiation, below 100 mSv, may actually be positive or at least neutral to health, and suggest that the present LNT overestimates radiation risks. Therefore the dose-response particularly for low-doses and low dose-rates has to be further analyzed. The influence of genetics and genetic variation in individuals, as well as the response to high LET radiation is less clear. The objective of this study was to update the LNT debate by using the latest radiation biologic and epidemiologic data, as well as our predictions of the *Transformation Frequency-Tissue Response* (TF-TR) model. Low, chronic radon exposures are characterized by the occurrence of non-targeted effects (*e.g.* adaptive response, genomic instability) so their effect on the dose-response curve was simulated with the mechanistic, biologically-based TF-TR carcinogenic model. Model predictions were in agreement with the linear no-threshold hypothesis at high radon exposures, but dose-response curves for low, chronic radon exposures (less than 4 cGy) were slightly different.

*Key words:* low doses, ionizing radiation, health effects, LNT

### INTRODUCTION

Ionizing radiation arises from both natural and man-made sources and at very high doses can produce damaging effects in human tissue that can be evident

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within days after exposure (Cosma *et al.*, 2009). In the low-dose exposures, so-called late effects are produced many years after the initial exposure. Although low dose radiation exposure can potentially generate different kinds of biological risk, the risk of most concern is cancer. The *Linear No Threshold* (LNT) model assumes that, at low doses (in the range of near 0 up to 100 mSv), there is a linear dose-response relationship between exposure to ionizing radiation and the development of solid cancers in humans, the risk continuing in a linear fashion to lower doses without a threshold and that the smallest dose has the potential to cause a small increase in risk to humans (NRC, 2006). Current regulatory radiation protection limits are based on the LNT theory using health data from atomic bomb survivors. The validity of the LNT theory was debated in recent years, particularly at low doses. While most authorities, radiologic organizations agree that the LNT model is most appropriate, a number of studies have proposed radiobiological hormesis, suggesting that radiation levels of 100 mSv/year may actually be positive or at least neutral to health. The LNT is useful as a model for setting an upper limit on the amount of damage done by low doses of radiation, in order to set standards for acceptable radiation doses to personnel. It's a deliberately conservative approach, used in the absence of better data. In some cases, there is now data that indicates that the LNT is overly conservative. In others, there is still no data, so the LNT remains the appropriate model. Even in cases where the LNT is now known to be overly conservative, there is a general reluctance to relax standards. The dispute is not over the linear relationship at higher levels, but over whether the linear relationship ends at a certain threshold or the linear relationship continues all the way down to zero (or at least to undetectable levels).

Most regulatory scientific bodies (see Table 1) recommended the use of LNT, but admit, however, that a strictly linear dose response should not be expected in all circumstances. The most recent report (BEIR VII) of National Academy of Science – a regulatory body that provides a well considered opinion on issues like health effects of low exposures to ionizing radiation – clearly endorses LNT. The study carefully considered the evidence and rejected its relevance to the question of the dose response of humans (NRC, 2006). The National Council on Radiation Protection and Measurements (NCRP, 2002) states there is no conclusive evidence on which to reject the assumption of a linear-no-threshold dose-response relationship for many of the risks attributable to low-level ionizing radiation although additional data are needed. While many, but not all scientific data support this assumption (see Table 1), the probability of effects at low doses such as are received from natural background is so small that it may never be possible to prove or disprove the validity of the LNT assumption (NCRP, 2002).

Table 1

Major scientific bodies that have endorsed the LNT

Agency/Academy/Committee/Organization	Sustains LNT	Contradicts LNT
National Research Council of the National Academies (NRC, 1999; NRC, 2006)	*	
National Council on Radiation Protection and Measurements (NCRP, 2002)	*	
United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR, 2000)	*	
Canadian Nuclear Safety Commission (CNSC, 2009)	*	
International Atomic Energy Agency (IAEA, 2007)	*	
International Commission on Radiation Protection (ICRP, 2006)	*	
US National Radiation Commission (US NRC, 2006)	*	
US Environmental Protection Agency (US EPA, 2008)	*	
French Academy of Sciences (Tubiana <i>et al.</i> , 2005)		*
National Academy of Medicine (Tubiana <i>et al.</i> , 2005)		*

The advances in radiobiology during the past two decades, the understanding of carcinogenesis, and the discovery of defenses against carcinogenesis challenge the LNT model, which appears obsolete (Tubiana *et al.*, 2009a). Some scientists consider that the LNT hypothesis should be abandoned and replaced by a hypothesis that is scientifically justified and causes less unreasonable fear and unnecessary expenditure (Feinendegen *et al.*, 2005). The present LNT overestimates radiation risks, and the dose-response particularly for low-doses has to be improved (Aleta, 2009; Mitchel and Boreham, 2000). The French had many reactions to the LNT hypothesis and they had their own scientific body to issue a report on this matter. They found that there is lots of support for hormesis at the cellular level (Tubiana *et al.*, 2005). Experimental studies, *in vitro* or on animals, suggest the existence of a threshold (Tubiana, 2008). In the low-dose range (< 100 mSv), epidemiological surveys do not bring any convincing data in favour of a LNT relationship (Tubiana, 2008). Cohen (1998) concluded that the most plausible explanation for the discrepancy is that the linear no-threshold theory fails, grossly over-estimating the cancer risk in the low dose, low dose rate region. There are no other data capable of testing the theory in that region. The French Academies report (Tubiana *et al.*, 2005) concluded that LNT and its use in assessing the risks associated with low doses are not scientifically based. There is some

epidemiological data suggesting that hormesis also exists in humans (Kaiser, 2003). The evidence that defence mechanisms against radiation induced carcinogenesis are stimulated at low doses is incompatible with the LNT model (Tubiana *et al.*, 2009 b). The premise of the LNT theory is also challenged by medical evidence and patients' testimonials regarding the effectiveness of radon spa treatments of various ailments, most notably rheumatoid arthritis, that are accumulating worldwide (Zdrojewicz and Strzelczyk, 2006). Sanders (2009) draws attention to biases in epidemiological research when using the LNT assumption. The high efficacy of defence mechanisms against radiocarcinogenesis, particularly when the tissue is not disorganized, can explain the lack of carcinogenic effect of contamination by small doses of radium or thorium which has been observed on radium dial painters or in patients injected with thorotrast (Hofmann *et al.*, 1990; Hofmann and Hornik, 1999). Even UNSCEAR (2000) admits that while the data can be reasonably fitted with a simple linear-quadratic function, the possibility of a threshold for doses up to about 10 mGy cannot be excluded.

In considering radiation induced cancer, there are two main approaches: biological and epidemiological. Since we cannot conduct experiments on humans, radiation effects on humans can only be assessed by tracking accidentally exposed people over a long term and analyze the relationships between dose and illness (epidemiological approach). Biological approaches consist of "in vivo" and "in vitro" studies. The hypothesis can be tested on biological mechanisms, however, whether research results are also valid for humans needs to be examined (GEPR, 2012).

#### **LOW DOSES OF IONIZING RADIATION AND THE CELLULAR RESPONSE FROM A BIOLOGICAL APPROACH**

Low doses cause a dual effect on cellular DNA: a) one is a relatively low probability of DNA damage per energy deposition event (that increases with dose), and at background exposures this damage to DNA is orders of magnitude lower than that from endogenous sources; b) the other effect at comparable doses is adaptive protection against DNA damage from many sources, depending on cell type, species and metabolism (Feinendegen, 2005). The probability of error during the repair of DSBs increases drastically when multiple breaks are present simultaneously (Rothkamm and Lobrich, 2002). At low doses and low dose rates the relevant biological damage would be produced by a 'single hit' because of the spatial and temporal sparseness of the events causing the damage (NCRP, 2002). Since cancer is considered to be monoclonal (single cell) in origin, this suggests that the dose-response is linear at low doses with no threshold (NCRP, 2002). However, it is possible that the whole organism may be more capable of repairing damage at low doses and low dose rates, which would modify the dose-response to a sub-linear curve (NCRP, 2002).

Low doses of ionizing radiation (IR) damage DNA but also activate cell defences: anti-oxidative mechanisms, DNA repair, adaptive responses, elimination of aberrant and preneoplastic cells, and immune reactions (Tubiana, 2008). The effectiveness of these defences decreases with the dose and is modulated by several time factors. The cell defence strategy varies with the dose, the irradiated volume and the damage inflicted on neighbouring cells (Tubiana, 2008). Many studies found that chronic-exposure to low level radiation may exert a protective effect upon cells (Feinendegen, 2005). Radiation-induced bystander response predominates at low doses of relevance to radiation risk analysis (<0.2 Gy) and therefore needs to be fully characterised (Prise *et al.*, 2003). An important aspect is that these responses saturate with increasing dose to the single target cell, thus the relative roles of direct and indirect (non-targeted) responses change with dose (Prise *et al.*, 2003). Adaptive protection causes DNA damage prevention and repair as well as immune stimulation, developing with a delay of hours, and lasting for days to months (Feinendegen, 2005). The involvement of competing processes at low doses may have important consequences for understanding the effects of low-dose exposure. All types of mutations commonly seen in human cancers can be induced by ionising radiation (NCRP, 2002). The magnitude of the mutagenic effect (per unit dose) varies with dose rate reaching a maximum in the range of 1-10 mGy/min, which corresponds approximately to the rate of ROS-inducing DNA damage during oxidative stress (Tubiana *et al.*, 2009b). At low doses reduction of damage from endogenous sources by adaptive protection maybe equal to or outweigh radiogenic damage induction. Thus, LNT hypothesis for cancer risk is scientifically unfounded and appears to be invalid in favour of a threshold or hormesis (Feinendegen *et al.*, 2005). The importance of adaptive responses was emphasized by the results of Azzam and colleagues (1994), Redpath and colleagues (2001), Schöllnberger and colleagues, (2007) demonstrating that low or chronic exposure to radiation can induce processes which protect the cell against naturally occurring as well as radiation-induced alterations that lead to cell transformation. This may in some circumstances reduce rather than increase cancer risk, a conclusion inconsistent with the linear no-threshold model of cancer risk from radiation. On the other hand, genomic instability may contribute to radiation-induced carcinogenesis and produce a non-linear dose-response, but insufficient information is presently available about this process (NCRP, 2002).

## **LUNG CANCER RISK SIMULATIONS FOR LOW EXPOSURES TO HIGH LET RADIATION**

There are recent available scientific researches that led to the discovery of several effects that showed nonlinear dose-response at low doses, putting the validity of the LNT model into question (Schöllnberger *et al.*, 2007). However,

most of such effects have been observed for low doses of **low** LET radiation. There is a great uncertainty and research is being developed for studying the health effects of low dose exposures to high LET radiation (*e.g.* alpha particles emitted by radon and radon progeny decay). A single alpha particle track can deposit tens of cGy while a single  $^{60}\text{Co}$ - gamma ray (low LET) will deposit, on average, about 1 mGy (Mitchel and Boreham, 2000). In this respect, the TF-TR model was used to simulate the dose-effect relationship for low doses of radon occupational and residential exposures. This is a mechanistic, biology-based model, in which the average dose was replaced by the number of cellular hits, and lung cancer risk is proportional to oncogenic transformation. It was described in detail elsewhere (Truta-Popa *et al.*, 2011). For the comparison of predicted lung cancer risk to epidemiological observations, the Czech uranium miner data for low exposures were selected (Tomasek *et al.*, 2008). Model predictions, epidemiological data and LNT are in excellent agreement (see Figure 1 and 2). The smallest epidemiological absorbed doses are 0.04 Gy and 0.18 Gy, so only one data point is strictly in the low dose-region defined by BEIR VII (2006).

### Adaptive Response

To incorporate the adaptive response mechanism into the analysis of the epidemiological data of Tomasek and colleagues (2008), two scenarios were considered i) only doses smaller than 0.2 Gy (the highest dose value used in the Iyer and Lehnert study (2002) are affected by the adaptive response, and, ii) all doses smaller than the normalizing dose of 0.675 Gy are affected by the adaptive response (see Figure 1).

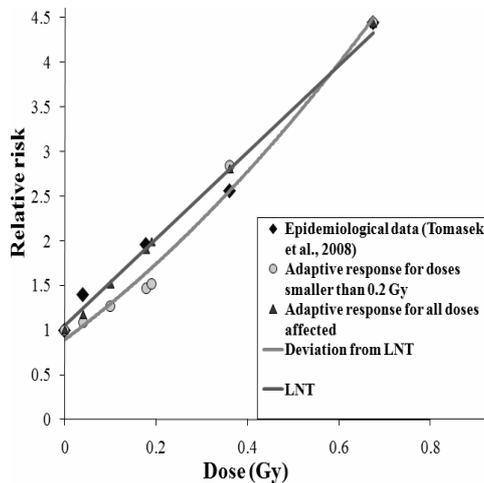


Fig. 1 – The impact of adaptive response on dose-effect relationship, for low, residential exposures.

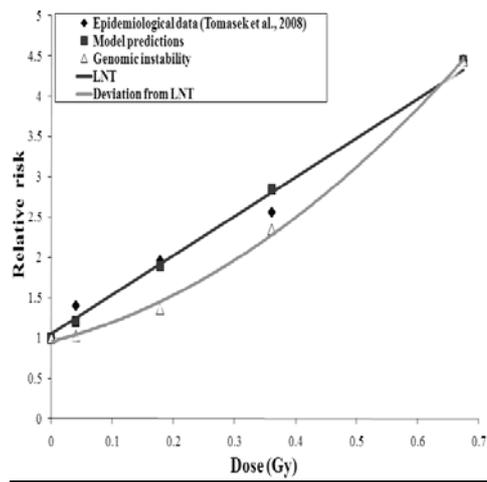


Fig. 2 – The impact of genomic instability on dose-effect relationship, for low, residential exposures.

The chosen normalization value of 0.675 Gy could be correlated with the threshold that has been reported by Rubino and colleagues (2003), at about 0.6 Gy - corresponding to doses per fraction of 20 mGy. Above this threshold, the dose-effect relationship appears to be quadratic (Rubino *et al.*, 2003).

### ***Genomic Instability***

A dose-response has been found for the dose-range of 0.5–2.0 Gy of low LET radiation (Streffer, 2010). Since we were interested in the effect of genomic instability (GI) for dose regions lower than 0.5-0.7 Gy of alpha particles, two different scenarios were assumed: (i) that GI (occurring after generation 26) increases linearly with time, independently on dose, and (ii) the cancer probability increases in a linear fashion with dose. In general, non-targeted effects like GI amplifies the biological effectiveness of a given radiation dose by effectively increasing the number of cells that experience effects over those directly exposed to the radiation; on the other hand, adaptive response will decrease the risk values and thus can be considered as defence mechanisms against oncogenesis (Truta-Popa *et al.*, 2011). While these observation is related to the absolute number of lung cancer cases, the results of the present calculations suggest that their effect on the shape of the dose-response relationship may be different (Truta-Popa *et al.*, 2011). Indeed, genomic instability and adaptive response cause a substantial reduction of the risk at low doses.

## **EPIDEMIOLOGICAL APPROACH**

The epidemiological evidence for carcinogenic effects in human populations is considered to be limited compared to experimental data. At the same time, epidemiological data have high validity in that they represent the average risk in human populations resulting from the integration of all the biological processes that are part of the radiation carcinogenic pathway and that no generalisation from other species or biological systems is required (NCRP, 2002). On the one hand, GEPR (2012) states that most epidemiological research shows that there is no significant cancer risk increase under 100 mSv exposure. On the other hand, systematic analyses of pooled data from 7 North American (Krewski *et al.*, 2006), 13 European (Darby *et al.*, 2005) and 2 Asian (Lubin *et al.*, 2004) residential radon studies were undertaken to provide a more direct characterization of the public health risk posed by prolonged radon exposure, to assess directly lung cancer risk from indoor radon and not to derive it from extrapolations of high exposures. Estimates of Odds Ratios (OR) were similar to extrapolations from miner data and consistent with published residential radon studies in North America and Europe, suggesting that long-term radon exposure at low concentrations found in many homes increases lung cancer risk (Lubin *et al.*,

2004). Their results showed a linear increase of lung cancer relative risk in the range of 8–16 % for prolonged exposure (30 y) per each 100 Bq m<sup>-3</sup> increase of average radon concentration (Darby *et al.*, 2005; Krewski *et al.*, 2006; Lubin *et al.*, 2004). The risk increase is statistically significant also restricting the analysis to cases and controls exposed to average concentrations  $\leq 200$  Bq m<sup>-3</sup> (Darby *et al.*, 2005). These combined analyses represent an important complement to the findings of the miner studies and further support the linear no-threshold model for cancer risk adopted by the BEIR VI Committee and other groups. In response, Tubiana *et al.* (2009 a) notes that as epidemiological data are inaccurate at low doses, one may fit them with a linear relationship, a linear-quadratic response relationship, a threshold somewhere between 40 and 60 mSv or even a hormetic response relationship. Studies on people exposed to radon at home included individuals who receive more than 100 mSv and thus are biased. For doses less than 100 mSv, cancer excess has not been observed, it is possible to be too small to be detected, but suggests that the carcinogenic risk if exists, should be very low and of a debatable importance (Tubiana *et al.*, 2009 a). Scientists tend to consider only statistically significant results. Many studies, therefore, apply regression lines and show that the slopes of excess relative risks are significantly greater than zero. That does not mean that cancer risks are significantly greater than zero in low dose areas. It is a limitation of epidemiology, which cannot claim that low dose radiation is not harmful, because researchers cannot control other factors that are assumed as error terms, even with such LSS data with many samples (GEPR, 2012). The committee of BEIR VII (NAS, 2006) concludes that the assumption that any stimulatory hormetic effects from low doses of ionizing radiation will have a significant health benefit to humans that exceeds potential detrimental effects from the radiation exposure is unwarranted at this time.

## CONCLUSIONS AND DISCUSSIONS

In conclusion, opinions differ regarding LNT hypothesis. Most regulatory organizations state that: 1) there is no evidence of a low dose threshold for radiation carcinogenesis, 2) that any stimulatory hormetic effect from low doses of ionizing radiation, having a significant health benefit to humans that exceeds potential detrimental effects from the radiation exposure is unwarranted, but 3) however, a strictly linear dose response should not be expected in all circumstances. LNT is not proven - indeed it is probably not provable at all - for low doses and dose rates, but it considers the most radiobiologically defensible assumption on which to base safety standards. It is a general rule that it is the best to follow the point of view adopted by most of the reliable regulatory bodies, rather than separate studies, particularly because they are more safe in what concerns health protection for the workers and the public. On the basis of epidemiological findings such as those of Darby *et al.* (2005), Krewski *et al.* (2006) and Lubin *et al.*

(2004) many international and national organizations have revised their recommendations and regulations on radon exposures in dwellings and workplaces, or are in the process to do so. In particular, both WHO (2009) and ICRP (2009) revised the upper limits for radon concentration in dwellings to  $300 \text{ Bq/m}^3$ , recommending an even lower limit ( $100 \text{ Bq/m}^3$ ) in places where this is achievable. However, NCRP (2002) states that the existing epidemiological data on the effects of low-level irradiation are inconclusive and, in some cases, contradictory, which has prompted some observers to dispute the validity of the linear-no-threshold dose-response model for extrapolation below the range of observations to zero dose. Although other dose-response relationships for mutagenic and carcinogenic effects of low-level radiation cannot be excluded, no alternative dose-response relationship appears to be more plausible than the LNT on the basis of present scientific knowledge (NCRP, 2002). Other organizations and scientists disagree with using the linear no-threshold model to estimate risk from environmental and occupational low-level radiation exposure, e.g. the French Academy of Sciences and the National Academy of Medicine published a report in 2005 that rejected the linear no-threshold model in favor of a threshold dose response and a significantly reduced risk at low radiation exposure.

Our model simulations of lung cancer risk induced by exposures to radon represent strong scientific evidence that at doses below 0.2 Gy, the shape of dose-effect relationship is not linear, but sublinear.

Taking into consideration the controversial, contentious debate on the LNT hypothesis, the American Nuclear Society (ANS, 2001) recommended further research on this issue before making adjustments to current radiation protection guidelines.

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